Cleveland Clinic

The Effect of Preoperative Patient Education: A Randomized Trial

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Study Protocol

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Summary of Changes:

May 12, 2021

1- Study title changed to “The effect of preoperative patient education: a randomized trial” (page 1)
2- Exploratory aim 2 is taken out on page 9
3- Laparoscopy assisted colorectal surgeries added in inclusion criteria on page 9.
4- For the brief introduction page, instead of “continue” or “stop” , patients will be presented the options “agree” or “disagree” (page 10)

December 1, 2021

1- A change in the inclusion criteria number 4 : from laparoscopic assisted **colorectal**, to laparoscopic assisted **abdominal** surgeries. (Page 9)

August 19, 2022

Sample sized increased to 760 after second interim analysis to compensate the technical data loss.

January 4, 2023

Sample size increased to 1060 after third interim analysis. As it was planned we re-estimated the coefficient of variation (CV) and assuming a 10% drop-out rate, we would need 1060 patients total.

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1) INTRODUCTION

a) Postoperative Pain Management

Approximately 45 million inpatient surgeries occur annually in the United States[1], postoperative pain continues to be a major issue. Surgical tissue injury causes pain, a psychological sensory experience, via various physiological factors. Among these is the nociceptive component, which results from activation of peripheral sensory neurons damaged by surgical incision, and the inflammatory component, which enhances pain sensitivity via release of mediators from the surgically injured tissue.[2] Central neuronal sensitization also apparently contributes to postoperative pain and hyperalgesia.[3]

Pain can present spontaneously during rest at the site of surgery and surrounding tissues. Furthermore, movement or touching of the wound site, breathing, coughing, and gastrointestinal motility can all evoke and aggravate pain. Unrelieved postoperative pain can even lead to complications including myocardial ischemia, impaired wound healing, delayed gastrointestinal motility, atelectasis, and postoperative pneumonia.[4-6] Furthermore, poorly controlled acute pain is strongly associated with the development of persistent incisional pain which can be devastating for patients.[7 8]

b) Opioids as Analgesics and Drawbacks

Opioids remain the mainstay pharmacologic approach to postoperative pain. However, sole reliance on opioid therapy is often inadequate. Most patients report moderate-to-severe pain after surgery despite being given on-demand analgesics.[9] In a 2014 survey, 86% of patients reported postoperative pain and 65% reported pain as

moderate to extreme.[10] Equally concerning is that 74% reported substantial pain even after discharge.[10]

Opioids are associated with multiple perioperative side effects. Many are due to the non-specific binding of opioids to various mu-opioid receptors throughout the peripheral and central nervous system. Such effects include nausea/vomiting, constipation, pruritus, urinary retention, ileus and respiratory depression.[11] [12] A remarkable four-fifths of adults given postoperative opioids report at least one opioid-related complications, with the most common being drowsiness (56%), constipation (35%), and nausea (28%).[10] The most feared complication is respiratory depression which is an important source of adverse events in hospitalized patients.[13] Respiratory depression is common in the postoperative period and is largely unrecognized, causing significant hypoxemia and potential harm.[14]

Opioids are also associated with post-discharge complications. Patients are typically given prescriptions for opioids to alleviate acute surgical pain but many continue to take opioids beyond their recovery period.[15-17] According to one study on opioid-naïve patients after total hip or knee arthroplasty, 8% of TKA and 4.3% of THA patients continued to use opioids 6 months after surgery. Among patients who used opioids at baseline, 53% of TKA and 35% of THA patients continued using opioids at 6 months.[18] Additionally, long term exposure to opioids may actually prolong pain after surgery by provoking hyperalgesia.[19] Chronic exposure to opioids is immunosuppressive and may augment infection risk.[20] [21]

Another terrifying aspect of long-term opioid use is the risk of tolerance and addiction by the patient, and misuse by the patient's family members, sometime encouraged by multitude of providers giving postoperative patients opioid prescriptions.[22] It is likely that all these factors contribute to the current opioid epidemic.[23]

i) Factors affecting postoperative analgesia

Postoperative pain is not simply a consequence of tissue injury. Instead, pain which by definition is a subjective sensation, is considerably influenced by patient

psychology. This is evident in cases where similar patients after similar noxious stimuli report very different amounts of pain and respond to analgesics differently.[24] [25] Personality is another major factor affecting how a patient perceives pain. In a study published by Conrad et al, 207 chronic pain patients were compared with pain-free controls. Patients were more likely to have a "harm avoidance" trait characterized by excessive worrying, pessimism, shyness, and being fearful and doubtful.[26] The same study reported that chronic pain patients also have a lack of cooperativeness and self-directedness, which is characterized by lacking a feeling of control and ability to positively alter their negative situations.[27] Translated to the perioperative population, patients with such traits may experience poor pain control despite treatments that usually suffice.

Patients with anxiety and depression also report high acute pain levels.[28] Another reason for the perception of "poor" pain control may be an unrealistic expectation of treatment efficacy. Most patients do not have preoperative pain; consequently, any postoperative pain at all may be perceived as unacceptable and therefore represent inadequate analgesia. In a recent systemic review by Hoffman et al, patients and the public "rarely had accurate expectations of benefits and harms of treatment, and … had a tendency to over-estimate its benefits and under-estimate its harms".[29]

ii) The Impact of Patient Education

There is abundant evidence that patient education improves clinical outcomes in various settings. Patient education programs improve outcomes for heart failure[30], chronic obstructive pulmonary disease,[31] diabetes[32], and many others medical conditions. Similarly, patient education initiatives are associated with improved outcomes after surgery. For example, enhanced stoma education incorporated into an enhanced recovery after surgery (ERAS) program shortened hospitalization after colorectal surgery.[33] A recent Cochrane review of 18 trials of preoperative education before hip or knee replacement surgery concluded that preoperative education may be a useful adjunct in certain patients including those with depression or anxiety.[34]

A recent randomized trial investigated the effects of preoperative opioid education on patients having shoulder surgery. Those with opioid education had significantly lower pain scores 2 and 6 weeks after surgery.[35] Additionally, patients assigned to opioid education used less narcotic 6-weeks and 3-months after surgery.[35] There is thus reason to believe that preoperative education focused on postoperative analgesia and opioid use might both improve pain control and reduce both short- and long-term opioid use.

Unsurprisingly, there is a strong correlation between patients' postoperative pain and their overall satisfaction with care.[36] Patients' expectations about postoperative pain are often unrealistic and influenced by emotions and past experiences. It is also common for patients to "catastrophize" pain sensations.[37] There is thus reason to believe that good communication and patient education might at least partially reduce pain scores and improve satisfaction.[38] Consistent with this theory, the Centers for Medicare and Medicaid (CMS) revised questions that assessed pain management from the Hospital Consumer Assessment of Healthcare Providers and Systems (HCAHPS) Survey in 2017. The questions now instead focus on how satisfied patients were with the hospital staff's communication regarding their pain.[39] Because reimbursement by Centers for Medicare and Medicaid Services is tied to patient experience and satisfaction, improved patient satisfaction with analgesic management may have economic value to hospitals.

In the context of the rising public concern about America's opioid epidemic, it is important for clinician to recognize and minimize the risk of opioids. Quality patient education on opioids, including both its advantages (analgesia) and disadvantages (short- and long-term complications), may help patients make better decisions about their use of opioids. Ideally, good preoperative education about pain expectations and wise use of opioids will reduce patients' dependence on opioids in the immediate postoperative period and after hospital discharge.

Consistent with this theory, a recent trial showed that opioid-related side effects and abuse potential in patients having orthopedic surgery was reduced by an education video on opioids during a 3-month follow-up period.[35] There is also evidence from a recent pilot study that preoperative education reduced pain levels during the initial 24

postoperative hours and resulting in fewer and less severe pain medication side effects, better functionality, and increased use of nonpharmacologic pain management.[40]

We thus expect that preoperative patient education will: 1) define realistic goals for pain relief and postoperative functionality; 2) promote the concept that some postoperative pain is normal and expected; 3) identify alternate analgesic modalities; and, 4) inform patients' decisions with respect to analgesia.

2) METHODS and STUDY DESIGN

A. Study Overview

We propose a randomized trial to be performed at the Cleveland Clinic. Patients will be assigned to: 1) an educational video focused on postoperative analgesia modalities, opioids, and realistic pain expectations (analgesic education); or, 2) an educational video focused on other aspects of the perioperative experience.

Specifically, the proposed research will have the following aims:

Primary Aim

To assess whether patients assigned to an analgesic education video have reduced short-term postoperative opioid consumption compared to those randomized to a generic education video.

Hypothesis: Our primary hypothesis is that patients assigned to analgesic education use less opioid between the end of surgery and the third postoperative morning (cumulative mg morphine equivalents).

Secondary Aims

Secondary Aim 1: To assess whether patients assigned to analgesic education (versus standard/generic) have better patient satisfaction with post-operative pain management.

Hypothesis: Patients assigned to analgesic education are more satisfied with pain management after surgery as measured on a 0-10 Likert scale (where 0 means not satisfied at all and 10 means completely satisfied) on the third day after surgery.

Secondary Aim 2: To assess the effect of analgesic education on postoperative pain during the first 72 post-operative hours or until discharge (whichever is earlier)

Hypothesis. Patients assigned to analgesic education have lower time weighted average pain scores during the first 72 post-operative hours or until discharge (whichever is earlier).

Exploratory Aim

Exploratory Aim: To evaluate the effect of analgesic education on composite of opioid-related complications including nausea, emesis, urinary retention, and ileus.

Hypothesis. Patients assigned to analgesic education have fewer composite of opioid-related side effects (i.e. incidence of emesis, nausea, ileus, urinary catheterization, and use of anti-emetics).

B. Setting and Population

i. Inclusion criteria

1. Modified informed consent;
2. Adults ≥18 years;
3. American Society of Anaesthesiologists physical status 1-4;
4. Scheduled for hip arthroplasty, laparoscopy assisted abdominal surgery;
5. In-person visit the PACE clinic;

6. Anticipated at least 24 hours stay after surgery;
7. Reasonable English fluency.

ii. Exclusion criteria

1. Opioid use for more than 30 consecutive days within three preoperative months, at a daily dose of 15 mg or more of morphine or equivalent. ;
2. Regional block or epidural analgesia.

C. Withdrawal Criteria

Patients will be free to withdraw from the study at any time.

D. Intervention

Patients will be given a tablet computer. Explanation of the trial, followed by a "agree" or "disagree" option will be presented. Those who continue will be assumed to have provided consent. If they select, "continue," the system then will randomize them. Patients will be randomized by computer 1:1 to either the treatment group or the control group at PACE clinic. Patients will be stratified according to chronic pain (chronic pain syndrome present). Randomization will be computer generated with random permuted block size 2 and 4, and allocation will be concealed. Caregivers and evaluators will be all masked to group allocation. The treatment group will receive a formal education presentation detailing realistic postoperative pain expectations and goals, the benefits and risks of opioids, wise use of opioids (lowest effective dose for the shortest time necessary), and non-opioid alternatives. In general form, it will be similar to the education video developed and used by Syed et al.[35] The control group will receive preoperative education regarding surgery per PACE clinic protocol on general preoperative education. Each educational tool consists of a ≈4-minute-long video that will be presented on a tablet computer during their preoperative visit and again shortly before surgery.

E. Protocol

Patients must meet all inclusion and exclusion criteria to be eligible for the study. After eligibility is confirmed, an investigator will randomize patients to "analgesic

education" or "general perioperative education". During the preoperative PACE visit, patients will be given a CCF-approved tablet computer that contains a brief introduction for the study, and "analgesic education" or "general perioperative education" videos which each of them takes 4 minutes.

An unblinded research fellow will see participating patients before in the morning of their planned procedures and ask them to again watch the original "analgesic education" or "general perioperative education" reinforcement. Anesthetic management will follow pre-established clinical and institutional guidelines, but not be otherwise be controlled. Premedication, type of anesthesia, regional blocks, and intraoperative and postoperative opioid management will all be left to the discretion of the attending anesthesiologist.

In the PACU and postoperative periods, patients will be managed at the discretion of the primary care team and anesthesiologist. Postoperative opioids will be provided per clinical routine**.** Administration of regional anesthesia (including neuraxial and nerve blocks) preoperatively or postoperatively will be at the discretion of the clinicians who will adjust analgesic management as necessary.

F. Measurements

Demographics and comorbidities (*Table 1*) will be obtained from electronic medical reports. Blinded clinical evaluators will query patients for outcomes. Clinicians including nurses will be blinded to study and will be required to perform routine clinical management after surgery. Patients will be followed for outcomes daily for up to 72 hours after surgery. Any opioids prescriptions at discharge will be at the discretion of the primary care team. Long-term outcomes including modified brief pain inventory scores and the use of analgesics will be collected 90 days after surgery by telephone.

Primary outcome is opioid consumption during the initial 72 hours after surgery, will be collected from electronic medical records if discharged will be approached by phone and converted to morphine equivalent. Differences in morphine equivalents of 20% or more will be interpreted as clinically meaningful.

Secondary Aim 1; satisfaction with post-operative pain management will be evaluated using a 0-10 Likert scale (where 0 means not satisfied at all and 10 means

completely satisfied) on the third day after surgery by phone by blinded clinical evaluators. Difference of 2 points in satisfaction will be accepted as clinically meaningful difference.

Secondary Aim 2; pain scores will be obtained from electronic medical records which are recorded by nursing, in PACU it is every 15 minutes and in ward every 4 hours while hospitalized. Difference of 1.2 points in pain scores will be accepted as clinically meaningful difference.

Exploratory Aim 1; composite of opioid related side effects and the antiemetic use will be obtained from nursing and medication notes from electronic medical records.

Exploratory Aim 2; analgesic use will be obtained from the Ohio prescription registry at 3 months.

Sex
Age (years)
Ethnicity
Height (cm)
Weight (kg)
BMI
ASA status
Surgery Type
Smoking status (current, former, never)
Medical History : Pulmonary disease, Kidney disease, Hypertension, Diabetes Mellitus, Neurologic disease, Coronary Artery Disease, Myocardial infarction, Chronic pain conditions, illegal drug usage, alcohol abuse, previous surgery or stent placement and medication usage

Table 1: Baseline and demographic characteristics

G. Statistical Plan and Sample size estimation

Analyses will be modified intent-to-treat, including all randomized patients who received treatment (i.e., patients randomized but not receiving treatment will not be included in the analyses). The treatment groups will be compared on baseline characteristics using absolute standardized difference (ASD), defined roughly as the absolute difference in means divided by the pooled standard deviation. Imbalance will be defined as an ASD of greater than 0.10. All the analyses will be adjusted for imbalanced baseline characteristics. The confidence level for all analyses is set at 95% ($p < 0.05$)

Primary Analysis

The effect of pre-operative patient education on cumulative opioid consumption (morphine equivalents) during first 72 postoperative hours will be assessed by using a t-test on the log transformed opioid consumption. Linear regression will be used to adjust for imbalance if necessary. The 95% CI for the ratio of geometric means (intervention/placebo) between the two groups will be reported.

Secondary Analysis

The effect of the intervention on patient quality satisfaction scores assessed on the third post-operative day will be determined by using a t-test or linear regression adjusting for imbalanced covariates as appropriate. If the distribution of patient satisfaction scores is skewed, we will use Wilcoxon rank-sum test or log-transformed scores to assess the effect.

The effect on time-weighted average pain scores during the first 72 post-operative hours will be assessed in a manner similar to that for patient satisfaction scores.

Adjusting for multiple testing using the Bonferroni correction, the secondary analyses will be carried out at the 97.5% confidence level (i.e. $p < 0.05/2$).

Analysis for Exploratory outcomes

The incidence of a composite of opioid-related complications will be assessed using a log-binomial model and reported as relative risk. The effect on opioid medication use (morphine equivalents) at three months after surgery will be assessed using a t-test or linear regression on the log-transformed opioid consumption. Covariate adjustment will be used to adjust for confounding as needed. The analyses will be carried out at the 95% confidence level.

Interim Analysis

Three interim analyses will be conducted at 25%, 50% and 75% of the planned enrollment to assess efficacy utility using a group sequential design with a gamma spending function (Gamma = -4 for efficacy and Gamma = -1 for futility) with non-binding efficacy and futility boundaries. The probability of crossing either the efficacy or futility boundary at the first, second and third interim analysis will be 9%, 40% and 78% respectively if the alternative hypothesis is true.

H. Sample Size Calculations

The coefficient of variation (CV) for cumulative opioid consumption was estimated to be 1.32 using a previous study[41]. However, for our sample size calculations, we assume a lower CV of 1.00 because--unlike the previous study--we will be excluding patients with a history of opioid use in the past 3 months.

Based on the primary outcome of cumulative opioid consumption during the first 72 post-operative hours and assuming a CV of 1.00 we would need a total of 588 patients to have 90% power to detect a 20% decrease in opioid consumption at the 0.05 significance level. Planning for 3 interim analyses and one final analysis, we would require a maximum of **672 patients.** The boundaries for the analysis [efficacy (futility)] are: $P \leq 0.002$ ($P > 0.926$), $P \leq 0.005$ ($P > 0.624$), $P \leq 0.015$ ($P > 0.2011$), and $P \leq 0.044$ ($P > 0.044$).

Internal Pilot Study to Re-assess Variability in Primary Outcome. The coefficient of variation will be re-assessed via an internal pilot study at 50% of the planned enrollment, and sample size will be increased if needed. For a CV of 1.32 and planning for three interim analyses and one final analysis, we would need a maximum of **974 patients.**

Second interim analysis re-assessment:

Based on the results of the second interim analysis executive committee suggested to increase the sample size to **760 patients** to compensate the technical data loss.

Third interim analysis re-assessment:

It was planned that we would re-estimate the coefficient of variation (CV) at 50% of planned enrollment. From the current sample of patients, the CV was estimated as 1.30 (up from 1.00). Using the re-estimated CV and assuming a 10% drop-out rate, we would need 1060 patients total (530 in each group) in order to have 90% power to detect a geometric mean ratio of 0.80 at a significance level of 0.05.

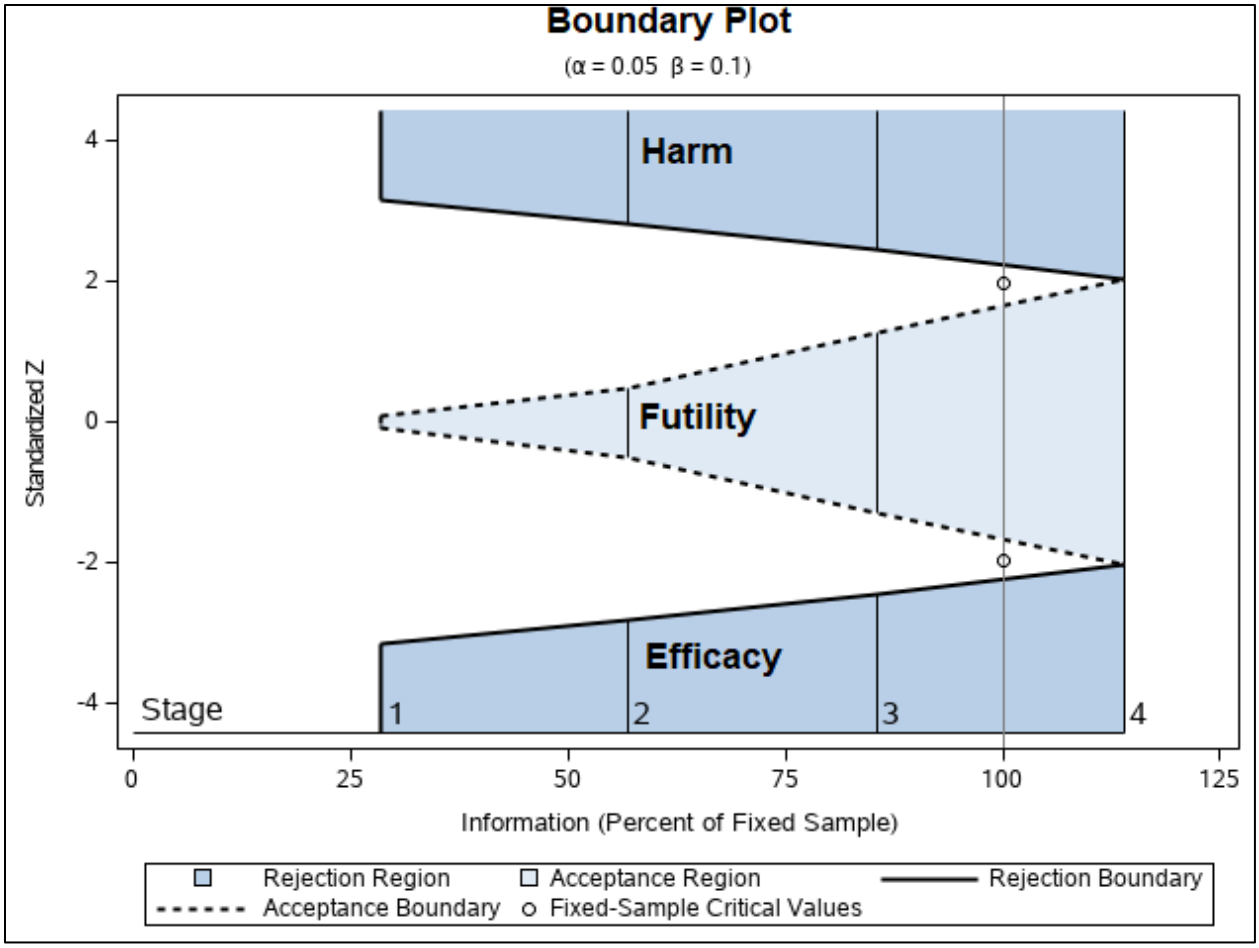

Figure 1: Efficacy and futility boundaries (non-binding) for the study design

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